Sealing techniques for pituitary tumour surgery – does it influence resource use and complications?

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15th of May 2009

FOREWORD

This study was initiated by Nycomed Pharmaceutical Norway. The company aimed at obtaining more information on Tachosil® which is a product that is used during surgery to stop bleeding or leakage of cerebrospinal fluid. Nycomed offered the project to master students who could use the study for a master thesis. Nycomed offered a student grant for the student who chose the project.

The initial aim of the project thesis was to perform a full economic evaluation of Tachosil® in relation to a comparator, with patient data from Ullevål University Hospital. A meeting, which included my supervisor, my contact person from Nycomed, a neurosurgeon at Ullevål, the head of the Neurosurgical department at Ullevål and me, took place in October 2008. Together we decided that an economic evaluation of Tachosil® used in transsphenoidal surgery when removing pituitary tumours would be my topic for the thesis. Two additional meetings took place between November and January, at which we discussed the needed data material more in detail. Since I was not allowed access to patient records, an assistant resident physician was funded by Nycomed to go through the relevant patient records, a total of 82, and to find the information that would be relevant for my thesis. I received the data material in February, and unfortunately the data showed that Tachosil® only were used in 13 operations, thus the distribution of patients between the groups were unequal. For that and other reasons, a full economic evaluation turned out to be impossible.

I would like to acknowledge the following for providing valuable information: Zinajda Zolic and Nycomed, Aqeel A Chaudhry, Roger Josefsen and Glenn Knutsen. I would like to thank my supervisor Ivar Sønbø Kristiansen (MD PhD MPH, at The Institute of Health Management and Health Economics, University of Oslo) for sharing his valuable time and wisdom. Last but not least, my profound thanks go to my co-students; Katrine, Irina and Linn for all the laughs and coffee breaks we have shared during this master thesis period, and to my family for always believing in me.

Cecilia Therese Olofsson

Oslo, May 2009

ABBREVIATIONS AND ACRONYMS

ACTH	Adrenocorticotropic hormone
ADP	Adenosive diphosphate
AVP	Arginine vasopressin
CBA	Cost benefit analysis
CCA	Cost consequence analysis
CEA	Cost effectiveness analysis
CMA	Cost minimization analysis
CSF	Cerebrospinal fluid
CUA	Cost utility analysis
DALY	Disability adjusted life year
DI	Diabetes insipidus
FSH	Follicle stimulating hormone
GH	Growth hormone
HrØoL	Health related quality of life
ICER	Incremental cost-effectiveness ratio
ICU	Intensity care unit
LH	Lutenizing hormone
NSB	Net social benefit
OR	Odds ratio
OT	Oxytocin
PRL	Prolactin
ØALY	Quality adjusted life year
RCT	Randomized controlled trail
RR	Relative risk
SG	Standard gamble

SWC	Standard ward care
TSH	Thyroid hormone
TSS	Transsphenoidal surgery
TTO	Time trade-off
WTP	Willingness to pay

ABSTRACT

Background: Cerebrospinal fluid leakage and other complications followed from transsphenoidal surgery when removing pituitary tumours are rare but serious. Through studies and clinical trials, Tachosil® has proven to be an effective sealing agent, thus in preventing complications.

Methods: Data of 82 patients that underwent transsphenoidal surgery for removing pituitary tumours in Ullevål University Hospital in the years 2006-2008 was collected. Statistical tests were performed to test the differences between the sealing techniques used during surgery in terms of patient characteristics, complication rates and length of stay. Costs expressed in 2009 NOK of the sealing agents (Tachosil® and Neuro-Patch®), intensity care unit and standard ward care were identified.

Results: The complication rate was 25% in the Neuro-Patch® group and 23% in the Tachosil® group (p=0.726). The mean ICU LOS in the Tachosil® group was 1.42 days and SWC LOS was 5.92 days, while the numbers were 1.93 and 7.93 in the Neuro-Patch® group. The differences between the two groups according to length of stay were not statistically significant. The mean ICU cost of a patient in the Neuro-Patch® group was NOK 52,200 and NOK 38,250 in the Tachosil® group (p=0.265). The mean SWC cost in the Neuro-Patch® group was NOK 38,080 and NOK 28,400 in the Tachosil® group (p=0.856). The mean cost of the sealing product was NOK 394 in the Neuro-Patch® group and NOK 1,261 in the Tachosil® group (p<0.001).

Conclusion: The results of this study do not provide any evidence that Tachosil® is superior in terms of complications or length of stay.

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1. Introduction

The history of neurosurgery goes back thousands of years (Mellergård, 1998). The oldest known surgical procedure is trepanation in which a hole was drilled into the skull to treat intracranial diseases. It is also believed that trepanation was used for mystical practices; to release tormented spirits. Evidence of trepanation is found in prehistoric human remains, suggesting that this procedure was used as early as during the later part of the Stone Age, around 6500 BC (Trepanation, 2009). Signs of structure healing on many of the skulls suggest that several "patients" actually survived the operations. Skulls with trepanation have been found in England, France and other European countries, as well as in Africa and South America (Mellergård, 1998). The earliest written documentation of neurosurgical practices are the so called "Edwin Smith Surgical Papyrus", which is a copy of a text originally issued 2500-3000 years BC. The text includes descriptions of the anatomy of the brain and procedures of head traumas. Around 400 BC, Hippocrates "the father of medicine" made elaborate observations of head traumatized patients and also indicated the use of trepanation. Some of his observations and ideas are still relevant today.

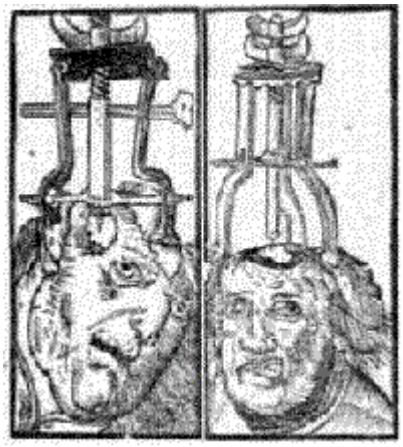

Figure 1: Engraving of trepanation by Peter Treveris 1525

The birth of the modern neurosurgery is often dated to the year 1879 when the Scottish William Macewen performed a historical intracranial operation of a left frontal meningioma on a young woman with focal epileptic signs (Mellergård, 1998). The operation was successful and the woman lived for eight more years. During the following years he performed many successful operations, and he earned himself a well-deserved reputation. An Englishman called Sir Victor Horsley is another well-known pioneer in neurosurgery, who started his career as a surgeon at John Hopkins hospital in Baltimore after performing

hundreds of brain surgeries on monkeys. In 1887 he became the first physician to remove a spinal tumour, but he also became known for a number of technical innovations, including the haemostatic bone wax. While both Macewen and Horsley were general surgeons, Harvey Cushing from America consolidated neurosurgery as a speciality. The main part of his working life in the beginning of the 20th century was spent at Peter Bent Brigham Hospital in Boston and as a teaching professor at Harvard Medical School. He developed many of the basic surgical techniques for operating on the brain and became the worlds leading teacher of neurosurgeons. His most famous discovery is the Cushing's disease in 1932.

Neurosurgery entails many risks including bleeding, paralysis, cerebrospinal fluid leakages, brain damages, infections, various other complications and deaths. Two milestones in the improvement of outcomes from surgery were the introduction of anaesthesia and aseptics. Due to more recent technologies, interventions and a higher level of expertise, neurosurgeons are now able to perform more complex procedures at lower morbidity and mortality rates (Matula and Steiger, 2005). In the following, I will explore technologies that are used to prevent bleeding and cerebrospinal fluid leakage and thus reduce the risks from neurosurgery.

1.1 Haemostasis

Haemostasis contains those mechanisms that contribute to halt bleeding after tissue injury (Bjålie et al, 2003). It is necessary that these mechanisms work optimal to avoid serious blood loss (ineffective mechanisms) or unwanted blood coagulations (hyperactive mechanisms).

Haemostasis can be divided into three processes (Berkow et al, 1997):

* Constriction of the injured blood vessel

* Activation of the platelets

* Activation of a number of blood clotting factors

The blood platelets have a central role in the haemostasis (Bjålie et al, 2003). When a vessel is injured, they form a plug that mechanically halts the bleeding, but they are also of great

importance during the other steps of the haemostasis. The blood vessels inner surface is normally smooth and unresponsive. When this inner surface is injured, it becomes reactive and the haemostatic mechanisms are triggered.

When injured, the blood vessel immediately constricts so that the blood flow is reduced and the clotting can start. This constriction can last up to half an hour. The platelets are activated and a number of reactions start as soon as the vessels wall breaks. A plasma protein called von Willebrand factor is produced by the cells of the vessels, working as glue to make the platelets stick to the injured area. The platelets bind to collagen[1] in the exposed walls of the blood vessel, releasing adenosine diphosphate (ADP)[2] which causes the platelets to swell and aggregate (Hakim & Canelo, 2007). Further more, the platelets form thromboxane A_2[3] which helps to make the platelets more adhesive. The clotting continues until the injury is plugged. To make sure that the clotting is limited to the injured area and doesn't expand into the uninjured parts of the blood vessel, an enzyme called prostacyclin is released from the uninjured area, neutralizing the platelets activation (Bjålie et al, 2003).

The coagulation process involves sequential activation of a number of blood clotting factors, resulting in the formation of fibrin (Hakim & Canelo, 2007). First, when a blood vessel is injured, prothrombin (factor II) is transformed into thrombin[4]. Thrombin then converts fibrinogen[5] to fibrin, which is a protein consisting of inextricable threads, that ensnares blood cells for clotting in the injured area (Bjålie et al, 2003). When the tissue healing is present and there is no longer use for the clot, the clot will attract and stimulate the growth of fibroblasts and smooth muscle cells within the vessel wall, and begin the repair process. This process is called fibrinolysis and results in dissolution of the clot. A vessel that has been clotted is now open again.

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[1] Collagen is a fibrous structural protein that supports most tissues and gives cells structure from the outside, but it is also found inside certain cells.

[2] ADP is a nucleotide which is stored inside blood platelets. It is released when the platelets are activated.

[3] Thromboxane A_2 is an eicosanoid which is a lipid. It is produced by platelets to stimulate activation of new platelets as well as increasing platelet aggregation.

[4] Prothrombin is found in an inactive state in the circulation system. When a vessel is injured, an inactive enzyme called factor X is transforming prothrombin into thrombin.

[5] Fibrinogen is a plasma glycoprotein that are synthesised by the liver.

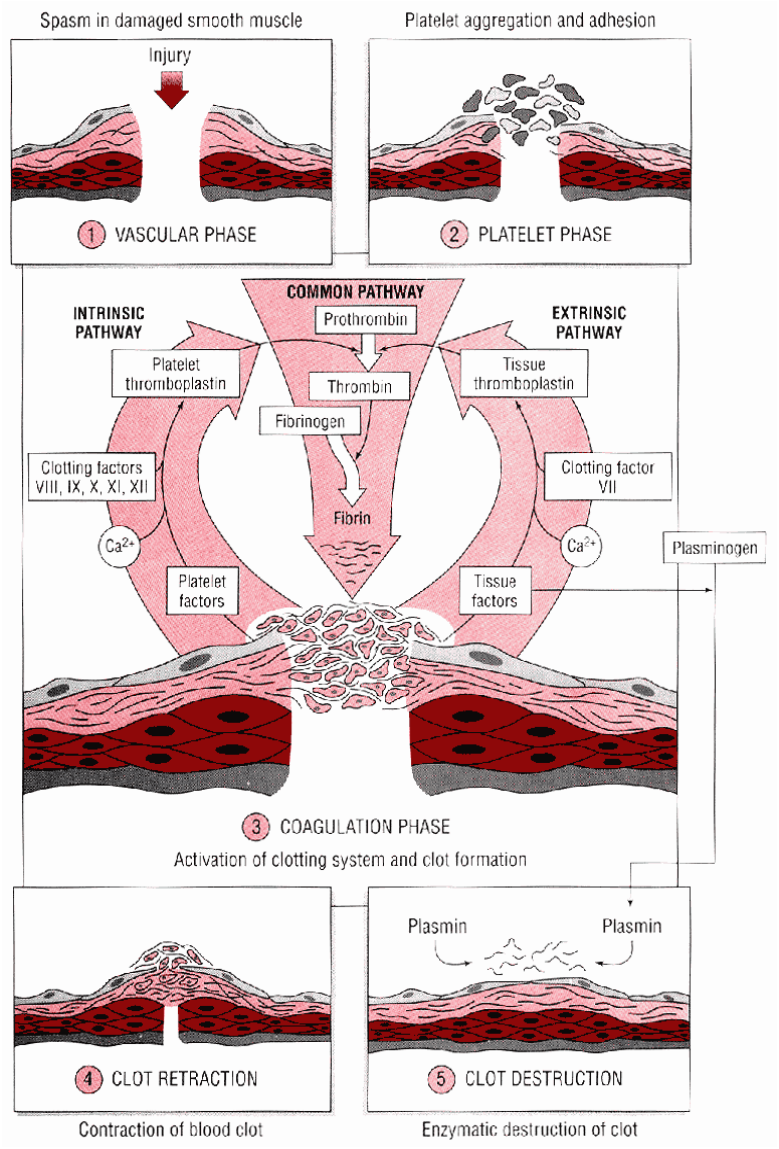


Figure 2: The different steps of haemostasis, from injury to the dissolution of the clot

1.2 Haemostasis in neurosurgery

In neurosurgery, absolute haemostasis is essential (Hakim & Canelo, 2007). Perioperative complications involving bleeding may have serious consequences as blindness or paralysis. In a prothrombotic environment, the haemostatic process might become pathological and lead to thrombosis[6]. More seriously, neurosurgical patients are at risk of thromboembolism[7],

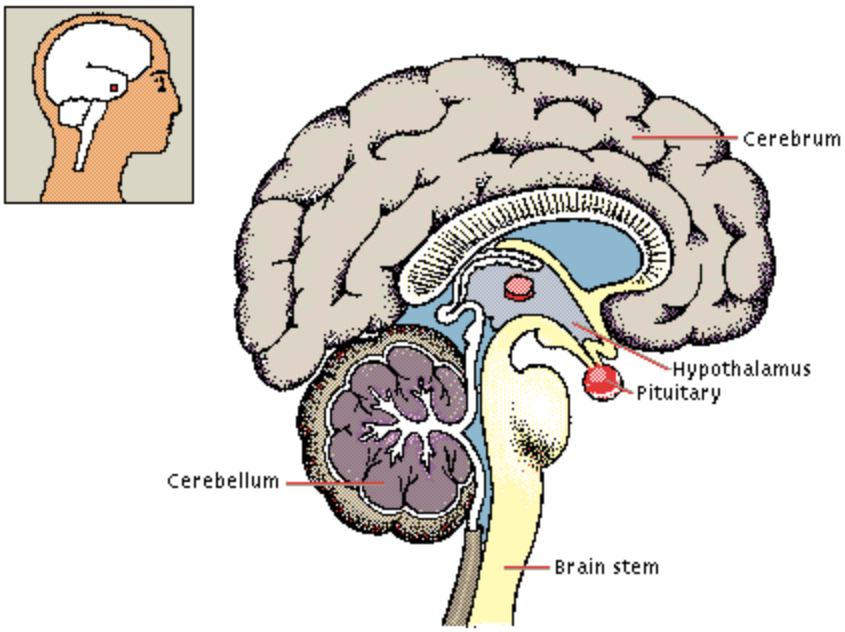
[6] If the haemostatic process causes too much clotting inside a blood vessel, obstructing the blood flow, a thrombosis is formed.

which may lead to cerebral infarction. Patients with brain tumors may be at increased risk from use of procoagulants such as steroids, chemotherapeutic and hormonal agents. It is also believed that the tumors themselves are able to secrete procoagulant factors. Since there is a limitation of laboratory tests that can identify those in a prothrombotic state, it is important to be aware of, and to identify the risk factors that can lead to thromboembolism.

1.3 Anatomy, physiology and function of the pituitary

Hypothalamus is a region located below the lower part of the brain (Molina, 2006). It is crucial in both the autonomic nerve system and the endocrine system. The coordination of the endocrine system is done with the help of the pituitary, which is a pea-sized gland situated below the hypothalamus (fig 3).

Figure 3: Location of the pituitary gland

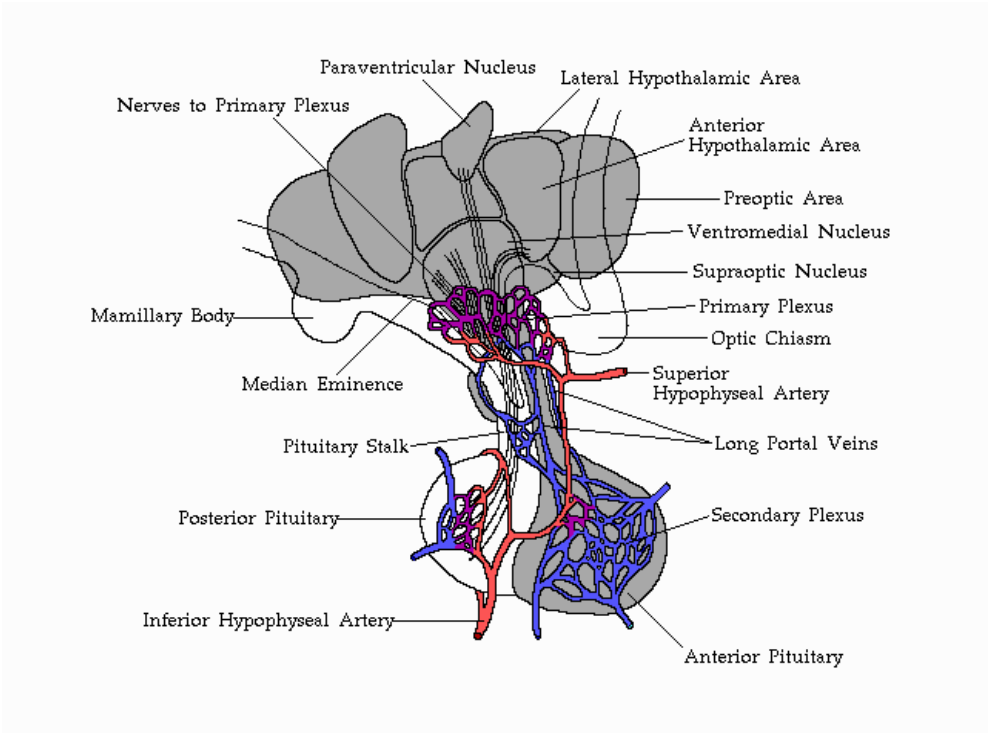


The pituitary is connected to the hypothalamus with the pituitary stalk and consists of an anterior (adenohypophysis) and a posterior lobe (fig 4). The posterior pituitary, which is the smallest one, consists of nerve fibres, glial cells and blood vessels, and is a part of the

[7] Thromboembolism is when a thrombus migrates from one part to another part (emboli), where it causes a blood blockage.

central nervous system. There are no hormone producing cells in the posterior pituitary, thus its hormones are produced in the hypothalamus. Instead it serves as a storage place for two peptide hormones called arginine vasopressin (AVP) and oxytocin (OT), produced in magnocellular neurosecretory cells of the hypothalamus. The releasing of these two hormones to the vessels and further transported into the body, depends on multiple reflexes and stimulation from neuroendocrine cells. AVP is most important for the function of the kidneys, since it regulates the body's retention of water (Bjålie et al, 2003). But it is also involved in the haemostatic process, making the blood vessels constrict when injured. Oxytocin plays an important role in the female reproduction as it evokes constrictions in the uterus during birth, and it facilitates breastfeeding by pressing the milk through the canals when the nipples are stimulated.

Figure 4: Anatomy of the pituitary gland



In contrast to the posterior pituitary, the anterior pituitary produces its hormones (Molina, 2006). The pituitary stalk consists of a portal system (two capillary beds connected by small blood vessels) that links the anterior gland and the hypothalamus. The first capillary bed, located in the hypophyseal portal system of the pituitary stalk, receives transmitters from neurocells found in the hypothalamus. These neurocells are taken by blood vessels to the second capillary bed in the anterior pituitary where they bind to specific receptors of

hormone producing cells, then activated, released and taken by blood vessels to specific target cells. The anterior pituitary consists of many types of endocrine cells that produce different peptide hormones (Bjålie et al, 2003).The most important ones and their functions are summarized in Table 1. Several of these hormones stimulate, sometimes in addition to other functions, the production of other hormones.

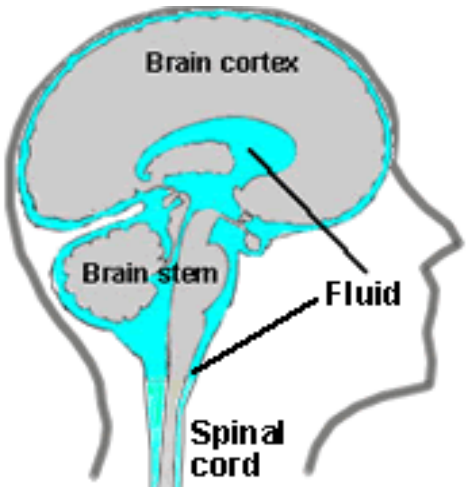
Table 1: The hormones of the anterior pituitary

Hormones	**Function**
Adrenocorticotropic hormone	Stimulates the secretion of steroid hormones (cortisol) in the adrenal cortex
Beta-endorphin	Inhibit pain
Human growth hormone	Stimulates growth
Thyroid stimulating hormone	Stimulates the secretion of thyroid hormones in the thyroid gland
Follicle stimulating hormone	Stimulates reproduction in the gonads
Luteinizing hormone	Stimulates reproduction in the gonads
Prolactin	Stimulates milk production in the mammary gland

1.4 Cerebrospinal fluid

The cerebrospinal fluid (CSF) is a colourless and clear fluid that occupies the surface of the central nervous system; more specifically it occupies the subarachnoid space which is the interval between the arachnoid mater and the pia mater[8], and is contained within a system of fluid-filled cavities called ventricles (Bjålie et al, 2003; Cerebrospinal fluid, 2009). Compare to blood plasma, the concentration of glucose is smaller and there is much less protein. The ion composition is also different, made for optimal function of the neurocells. The CSF flushes through the nervous system, reproduced several times a day. The total volume of CSF in an adult human is about 150 ml, while 500 ml is produced every day. CSF is produced in the choroid plexus (the lateral ventricle), and further transported to the third ventricle through the interventricular foramen, which is also called the foramen of Monro. The fluid continues its way to the fourth ventricle, passing through the cerebral aqueduct (also called the Aqueduct of Sylvius), that serves as a link between the third and fourth ventricle. CSF then exits through the foramina of Luschka, of which there are two, and the foramen of Magendie, and is finally absorbed into the blood stream through structures called arachnoid villi, which are located along the superior sagittal sinus.

Figure 5: Cerebrospinal fluid



[8] The pia mater, arachnoid mater and dura mater are the three meninges which is a system of membrane that envelops the central nervous system, mainly for protection.

1.4.1 Function of the cerebrospinal fluid

Functions of the CSF include (Bjålie et al, 2003; Cerebrospinal fluid, 2009):

- The CSF has the important role of protecting the brain from damage, as it works as a shock-absorber from blows against the head.
- Since the brain is "floating" in CSF, the weight of the brain is greatly reduced, which reduces the pressure at the base of the brain. Also, there is little room in the skull for the brain to increase its volume (cerebral oedema). Then, to hinder pressure damages, CSF is drained away.
- The CSF also protects the brain by functioning as an excretion of waste products, transporting damaging substances away from the brain and into the blood.
- Hormones are transported, with the help of CSF, to areas of the brain where they may act.

1.5 Pituitary tumours

Pituitary tumours constitute about 8% to 15% of all surgically treated intracranial neoplasm (Helseth et al, 2003; Rumboldt, 2005). Most pituitary tumours are adenomas[9] (Delellis et al, 2004). If a pituitary tumour is relatively large (macroadenoma) it can put pressure on the rest of the normal pituitary and nearby structures causing vision loss, headaches, nausea, seizures, loss of normal anterior pituitary hormone production and more. There is great variation in size[10], speed of growth, invasive growth and clinical features (Helseth et al, 2003). Pituitary adenomas can be classified as functional or non-functional depending on if it is hormonally active. Approximately 75% to 80% of pituitary adenomas are hormonally active (Rumboldt, 2005).

[9] Adenomas are noncancerous, nonspreading growth.

[10] Microadenoma (<10 mm), and macroadenoma (>10 mm).

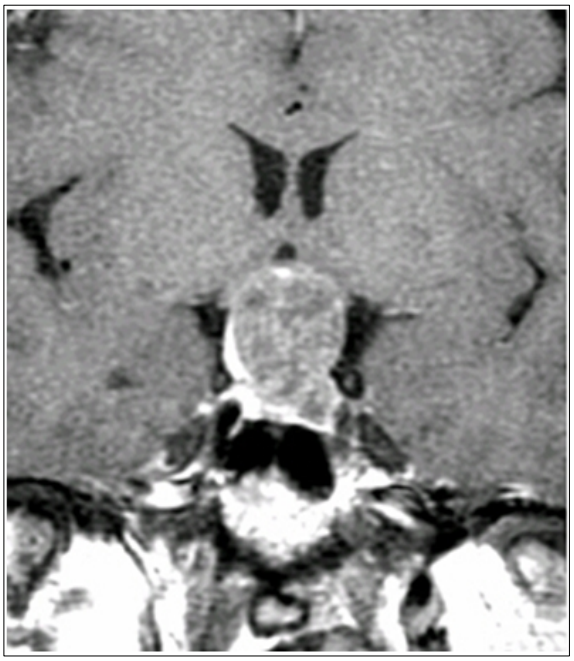


Figure 6: Pituitary tumour

1.5.1 Growth hormone producing adenoma

Growth hormone (GH) producing adenomas account for approximately 15-20 % of all pituitary adenomas (Helseth et al, 2003). They are clinically associated with either gigantism or acromegaly, depending on age of the patient at the start of the disease (Delellis et al, 2004). Gigantism is usually occurring in younger patients, characterized with excessive growth and height above average. Signs of acromegaly are often missed for many years, since the disease has a slow progression. Acromegaly commonly affects adults in their thirties but often the diagnosis and treatment are delayed for 6 to 12 years. Typical signs of acromegaly are enlargement of hands, feet, nose, lips, tongue and ears, thick and sweaty skin, soft tissue swelling of internal organs (kidney, weakening of muscularity of the heart), overgrowth of skeletal tissues, peripheral arthropathy (complication of inflammatory bowel disease), severe headache, loss of vision and more.

1.5.2 Prolactin producing adenoma

Prolactin (PRL) producing adenomas are usually very small and the mortality rate is low (Delellis et al, 2004). They account for approximately 25-30 % of all pituitary adenomas and are the most common pituitary adenoma in childhood and adolescence, more common among young females than young males (Helseth et al, 2003). They often appear later in life for men, thus often in the form of macroadenomas. PRL producing adenomas produce an

excess of the hormone prolactin, which can cause a decrease in normal levels of sex hormones[11], affecting men and women differently.

1.5.3 Thyroid producing adenoma

The TSH producing adenomas are very rare, with an account of 1% of the pituitary adenomas (Delellis et al, 2004). There is often a delay in diagnosis, since the signs are few, which causes the adenomas to be invasive and aggressive (often macroadenomas). An overproduction of the thyroid hormones (thyroxine and triodothyronine) is called overactive thyroid disease or hyperthyroidism, and can cause an overstimulation of the metabolism. This may result in sudden weight loss (from diarrhoea), fast heartbeat, irritability and anxiety.

1.5.4 Adrenocorticotropic producing adenoma

The ACTH producing adenoma stimulates the adrenal gland to produce more cortisol (Delellis et al, 2004). This condition is called Cushing's disease, the incidence is about 1-10 new cases per million, and it represents 10-15 % of all pituitary adenomas (Helseth et al, 2003). The ACTH producing adenomas usually appear between the ages of 30 and 40 years and are rare in childhood. Most ACTH producing adenomas are small microadenomas, but macroadenomas do appear. The signs and symptoms of Cushing's disease may include weight gain in the abdomen and facial roundness, high blood pressure, steroid induced osteoporosis, thinning of the skin and stretch marks, insulin resistance (which may lead to diabetes mellitus), growth of fat on the back of the neck (a hump), easy bruising, polyuria, muscle weakness, depression and anxiety, and more.

1.5.5 Gonadotropin producing adenoma

Pituitary adenomas that produce an excess in follicle-stimulating hormone (FSH) and/or lutenizing hormone (LH), represents 3-5 % of all pituitary adenomas (Helseth et al, 2003). They usually do not cause symptoms, most of them are hormonally inactive, hence difficult

[11] Estrogen in women and testosterone in men.

to diagnose (Delellis et al, 2004). But visual disturbances, hypopituitarism and headaches do occur. They are especially difficult to diagnose in women, since the level of FSH increases after menopause. When diagnosed, the adenomas are often large invasive macroadenomas.

2. Transsphenoidal surgery

Transsphenoidal surgery is the standard method, since the 1950s and 1960s, when removing pituitary tumours (Fatemi et el, 2008). The approach is through the sphenoid sinus which is the space behind the nose, from where the pituitary gland is accessible. Two variants of TSS is possible; the sublabial transseptal technique is to make an incision under the upper lip along the gum line and go through the base of the nose, and the transnasal technique is to go directly through the nose. The first TSS method being introduced was the sublabial transseptal method. However, in 1988, due to patient discomfort and mucosal traumas, the direct endonasal method was introduced, and is now the more common method.

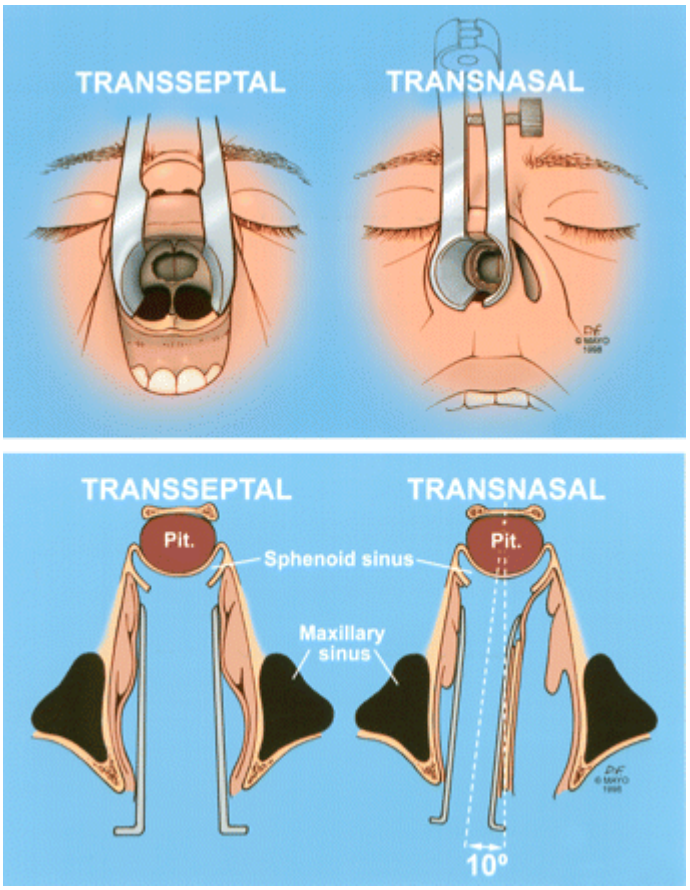
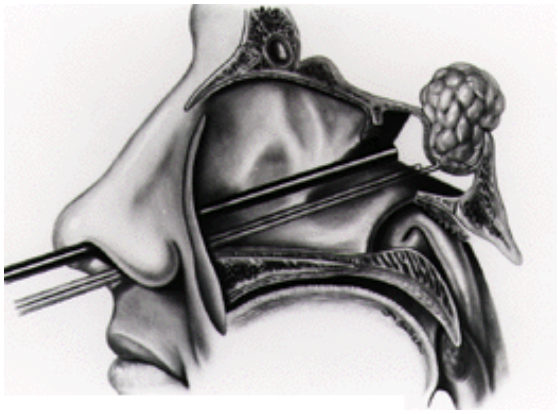


Figure 7: Transseptal versus transnasal technique

TSS has evolved dramatically over the years, making it safer to remove both microadenomas and macroadenomas according to morbidity and mortality (Black et al, 1988). Due to improved endoscopes and adoption of advanced surgical techniques, the endoscopic

transnasal approach has been developed, providing a minimally invasive route and suggesting shorter hospital stay (Atkinson et el, 2008; Fatemi et al, 2008).

Figure 8: Endoscopic transnasal approach



2.1 Complications

TSS is a reasonably safe procedure, suggesting a mortality rate of less than 1 % (Black et al, 1987; Ciric et al, 1997; Tamašauskas et al, 2008). However, complications that may result in serious consequences do appear.

2.1.1 Cerebrospinal fluid leakage

Postoperative CSF leakage, also called CSF rhinorrhea[12], is a serious and life-threatening complication (Tamašauskas et al, 2008). CSF leakage occurs when the meninges are damaged, usually as a consequence of head-trauma, surgical trauma or an invasive tumour (Han et al, 2008). If not treated in time, CSF leakage may lead to meningitis and, rarely, tension pneumocephalus and encephalopyosis, which are life threatening (Nishioka et al, 2005; Han et al, 2008). A number of studies have been made on the frequency of postoperative CSF leakage when removing pituitary tumours and its rate varies from 1% to 6% (Black et al, 1987; Cappabianca et al, 2002; Seiler et al, 2000; Tamašauskas et al, 2008; Han et al, 2008). The variation is suggested to be due to the experience of the surgeons, what

[12] Rhinorrhea, also known as"runny nose", has the characteristics of an unusually significant amount of nasal discharge.

kind of technology that was used, the size and type of the tumour and the sealing technique of the sella turcica. According to several studies, intraoperative CSF leakages occur more often than postoperative, with a rate that varies from 14% to 19% (Cappabianca et al, 2002; Nishioka et al, 2005; Tamašauskas et al, 2008; Han et al, 2008).

2.1.2 Diabetes insipidus

Diabetes insipidus (DI) is a condition characterized by an extreme thirst and excessive urination, which is caused by a disturbance in the secretion of the AVP hormone. Causes for DI include damage to the hypothalamus, head trauma, tumours and cranial surgery. Mortality is rare but other consequences such as severe hydration may follow if not treated in time. Not all cases of DI are permanent and can be treated with drugs. Tamašauskas noted 7 % transitory DI following TSS when removing pituitary tumours, compare to 2.8 % non-transitory (Tamašauskas et al, 2008). These rates seem to vary when comparing to other studies, but are consistent in that transitory DI is more common than non-transitory DI (Black et al, 1987; Ciric et al, 1997).

2.1.3 Meningitis

Meningitis is a serious condition that is caused by an inflammation of the meninges, usually caused by infection with microorganisms. There are different types of meningitis as well as different causes. During TSS, bacteria's from the nasal cavity may be entering the meninges area, and in some cases cause meningitis. Meningitis may also follow from CSF rhinorrhea. Meningitis following TSS for pituitary tumours is rare, studies suggest en incidence rate that varies from 0.4% to 2% (Black et al, 1987; Ciric et al, 1997; Tamašauskas et al, 2008). The first symptoms are usually severe headaches, fever, vomiting, neck stiffness, sensitivity to bright light and confusion. If not treated in time, meningitis may have serious consequences such as deafness, epilepsy, cognitive deficits, and even death.

3. Sealing techniques

Since the beginning of modern neurosurgery surgeons have been confronted with intra-and postoperative complications such as bleeding, CSF-leakages and infections (Matula and Steiger, 2005). Especially sealing of the dura mater has been hard to achieve.

There are various techniques for repairing the sella turcica when undergone TSS for pituitary tumours. Autologous tissues such as fat, muscle graft and fascial has in the last years been replaced by a variation of synthetic materials such as fibrin glue and different types of collagen sponges (Cappabianca et al, 2004; Kelly et al, 2001; Seda et al, 2006).

3.1 Tachosil®

Tachosil® (manufactured by Nycomed) is a ready-to-use fixed combination of a collagen sponge, produced from horse tendons, coated with a layer of the coagulation factors; human fibrinogen and human thrombin (Tachosil® product monograph, 2006). When applied to a surface of blood or other fluid, Tachosil® achieves haemostasis and sealing within 3-5 minutes. The patch can be cut in suitable pieces to fit small wound areas. Once Tachosil® comes in contact with liquid it becomes pliable and easy to apply, making it useful for hard-to-reach wounds. The patch comes in sterile packages, requires no preparations, and comes in three different sizes.

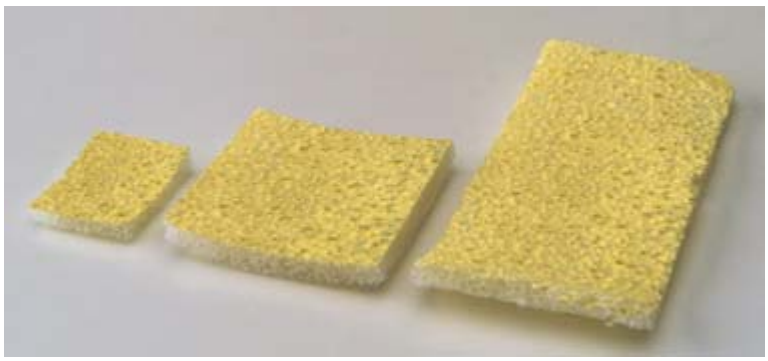


Figure 9: Three different sizes of Tachosil®. The yellow (riboflavin) colour shows the active side of the patch, which is coated with human coagulation factors

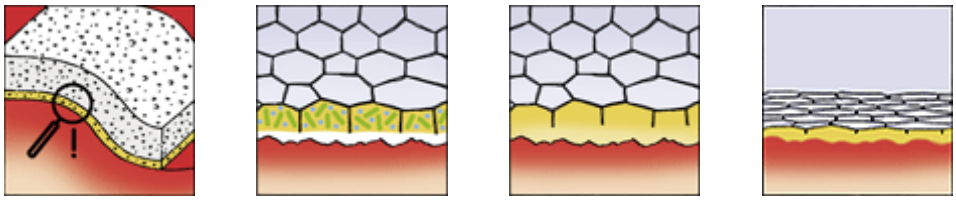


Figure 10: The mechanisms of Tachosil®. When the yellow side is applied on the wound (1), the coagulation factors are released (2) and fibrin is generated (3). The patch structure folds in, resulting in an air- and liquid- tight sealing of the wound (4). Tachosil® is absorbed by the body within 12 weeks of the procedure

Tachosil® is a further development of TachoComb® and TachoComb® H that was introduced to the market in the early 1990s (Matula & Steiger, 2005). Tachosil® differs from its predecessors in that it is free from bovine components, thus the risk of transmission of prions or other germs from cattle to patient is eliminated.

3.1.1 Earlier studies of Tachosil®

My search in the PubMed database for Tachosil® in randomized controlled trials resulted in four articles. S. Siemer et al conducted a randomized prospective study of the efficacy and safety of Tachosil® as a haemostatic treatment *versus* standard suturing in kidney tumour resection. A total of 185 patients were included in the study. The time to haemostasis was significantly shorter with Tachosil® than standard suturing (mean: 5.3 min *versus* 9.5 min [p<0.0001]) (Siemer et al, 2007). In the Tachosil® group, haemostasis was obtained within 10 min in 92% of the patients, compared to 67% in the standard treatment group (p<0.0001). There were no statistically significant differences in terms of safety and other secondary objectives, although surgeons considered Tachosil® to be more convenient to prepare and to apply.

An open randomized prospective trial to assess the effectiveness of Tachosil® *versus* argon beamer as a haemostatic agent during liver resection was reported in 2004 by A. Frilling et al. A number of 121 patients requiring secondary haemostasis during planned liver resection were included in the study. The study showed Tachosil® to be superior over argon beamer with regard to time to haemostasis (mean 3.9 min, median 3.0, range 3-20 min *versus* mean 6.3 min, median 4.0, range 3-39 min [p=0.0007]) (Frilling et al, 2004). There was a significantly shorter drainage period seen in the argon beamer group (mean: 5.7 days *versus*

8.2 days [*p*=0.005]). However, Frilling suggests that this could be due to the physicians being more cautious in removing drain from test patients (Tachosil®) than from patients who received standard treatment (argon beamer). There were no statistically significant differences in terms of adverse events.

Tachosil® has become an increasingly used approach during lung surgery. U. Anegg et al conducted in 2007 a randomized trial, including 152 patients, to investigate the efficiency of Tachosil® (TS group) *versus* standard therapy (ST group) for treating air leaks after lung resection. The 152 patients were randomized; 75 to the TS group and 77 to the ST group. The mean time to chest drain removal and mean time to hospital discharge was also investigated. A *t*-test for independent samples was performed, and a *p*-value <0.05 was considered to be significant. The mean intraoperatively post-treatment air leakage on postoperative days 1 and 2 was significantly lower in the Tachosil® group compared to the standard treatment group (153.32 ml/min, range 10-450 ml/min *versus* 251.04 ml/min, range 15-970 ml/min [*p*=0.009]) (Anegg et al, 2007). There was also a significant difference in the mean time to chest drain removal (5.1 days *versus* 6.3 days [*p*=0.022]) and time to hospital discharge (6.2 days *versus* 7.7 days [*p*=0.01]), both in the favour of the Tachosil® group. No significant differences in adverse events were observed. In 2008, Anegg et al presented a follow-up paper where the objective was to compare the costs of the materials and the costs of hospitalization between the two groups. They found an overall cost reduction of €98 in favour of the Tachosil® group (Anegg et al, 2008). Because the confidence intervals for the costs were wide, it could not be concluded that Tachosil® was superior over the standard treatment group.

Another prospective randomized trial on alveolar air leaks after pulmonary resection was conducted by A. Droghetti et al in 2008. One group of 20 patients received a combination of electrocautery treatment and Tachosil® (ES), and the other group of 20 patients had a routine surgical procedure with staplers (ST). The main goal was to compare the percentage of patients in the two groups who were free of air leaks throughout hospitalization. The incidence of air leaks in the first 48 hours in the ES group was 50% compare to 95% in the ST group (*p*=0.0001) (Droghetti et al, 2008). The duration of air leaks was 1.7 days in the ES group *versus* 4.5 days in the ST group (*p*=0.003). The procedure costs, timing of chest tube removal, complications and the length of hospitalization were compared as secondary objectives. Procedure costs were lower in the ES group (€425) compare to the ST group

(€630.5) (p=0.0001). There were no statistical significant differences between the groups in terms of time to chest tube removal, hospitalization and complications; however, there were indications of differences. Studies with larger sample sizes would be necessary to investigate these issues.

One study of the effectiveness of Tachosil® as a sealing agent after surgical removal of pituitary tumours was found in the PubMed database. The Department of Neurosurgery of Kaunas University of Medicine started in 1995 a prospective study of patients undergoing TSS for removing pituitary tumours (Tamašauskas et al, 2008). By 2005, 313 patients underwent 356 operations. The main objective of the study was to evaluate the frequency and the causes of intra- and postoperative CSF leaks and to discuss methods for closing the sella. The frequencies of other complications (meningitis, diabetes insipidus, and more) were also evaluated. 58 cases of intraoperative CSF leaks were observed, and for these cases; two different techniques for closing the sella were used. The first one was to pack the sella and the sphenoid sinus with autologous fat[13] and to restore the defect of the sella turcica with autologous bone, and the second one was to place Surgicel® on the defect of the sella membrane and a Tachosil® plate on top of it, then to pack the sella with autologous fat and cover the dura mater defect with Surgicel® and Tachosil®. Of the 29 patients in the first group, 12 experienced postoperative complications (41%), compare to 4 patients out of 29 in the other group (14%) (p=0.02). From this result, Tamašauskas concluded that the multilayer technique of using Surgicel® and Tachosil® was a reliable technique.

Table 2: Postoperative complications (Tamašauskas et al, 2008)

Postoperative complications	**Method 1**	**Method 2**
Postoperative CSF leak	3	0
Hypopituitarism	1	0
Sphenoidal sinusitis	2	0
Transitory diabetes insipidus	3	2
Permanent diabetes insipidus	2	1
Paresis *n. oculomotorius*	1	0
Intraventricular hemorrhage	0	1
Total	12 (41.4 %)	4 (13.8 %)

[13] Autologous fat refers to fat that are reimplanted in the same individual that it came from.

Several studies have been made evaluating the effectiveness of TachoComb® in neurosurgery as a dural repair agent. In 2002, M Reddy et al performed a retrospective review of 288 patients undergoing neurosurgery (operations on the brain, as well as spinal operations) where primary closure was not possible, using TachoComb® as a dural substitution. There were no cases of postoperative wound infections detected within a 32-months follow-up (Reddy et al, 2002). Postoperative CSF leaks were developed in five cases, rebleeding in one case, and subcutaneous CSF accumulation without leak in four cases. Reddy et al concluded TachoComb® to be an adequate alternative for dural substitution. Reddy et al presented in 2003 another retrospective study, this time using TachoComb® after primarily closure of the dura mater with sutures. Twelve patients out of 421 developed a subcutaneous CSF collection, thus TachoComb® was found to be an adequate agent for dural closure (Reddy et al, 2003).

3.2 Neuro-Patch®

Neuro-Patch® (manufactured by B. Braun Melsungen AG) is a type of microporous fabric made from a highly purified polyesterurethane, and is used as a dura mater substitution in neurosurgery (Neuro-Patch® product monograph, undated). To produce Neuro-Patch®, a dissolved polyesterurethane polymer is sprayed through electronically controlled specialised jets which cause a formation of uniform fibres. These fibres are captured at defined angles by a rotating cylinder, producing the basis of the fleecelike structure of Neuro-Patch®. In neurosurgery, the patch is fixed with non-absorbable suture material, and secured with fibrin glue. Neuro-Patch® can be cut into suitable pieces and comes in seven different sizes.

Neuro-Patch®, and the polyesterurethane used for production of Neuro-Patch®, has been tested in several animal experimental investigations, showing tissue tolerability and biostability. The patch has also been used as a dura mater substitute in clinical trials on humans, and has allegedly showed positive results when preventing CSF-leaks (Neuro-Patch® product monograph, undated).

4. Economic evaluation

Because of scarce resources available to spend, it is impossible to meet all demands (Brazier et al, 2007). This is true for most aspects of life, and health care is no exception. Economic evaluations are tools that are available for decision makers to help them make "right" decisions about how these resources should be spent. This aim is reached by identifying, measuring, valuing and comparing the costs and consequences of health care interventions (Drummond et al, 2005). There are three different approaches of full economic evaluation: Cost-Benefit Analysis (CBA), Cost-Effectiveness Analysis (CEA) and Cost-Utility Analysis (CUA). They all use monetary units when measuring and identifying costs, but differ in the way the consequences are being valued. A fourth approach called Cost-Consequence Analysis (CCA) is sometimes included.

4.1 Cost-Effectiveness Analysis

This approach measures health benefit in a non-monetary unit, for example life-year gained or the number of diabetes II prevented, and the result will be presented as cost per health benefit. Since CEA does not use generic measure of outcome, it is difficult to compare across studies. CEA is most often used in situations where a decision maker is operating with a given budget, and therefore has limited range of options (Drummond et al, 2005). The decision maker seeks to maximize the benefits within this given budget, by ranking the treatments or interventions according to their cost-effectiveness. The incremental cost-effectiveness ratio (ICER) is a term used in economic evaluation to compare the difference in cost and benefits of two or more treatments or interventions.

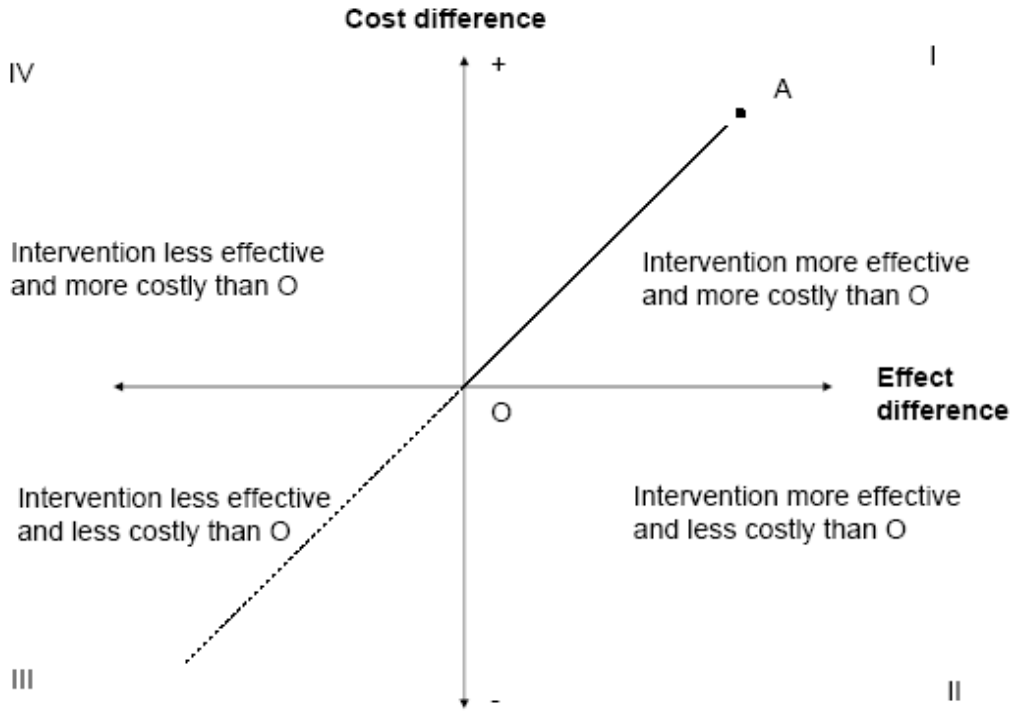
Equation 1:

$$\Delta C / \Delta E = \text{ICER}$$

Figure 11 represents two different interventions (A and O) and the difference in effect (horizontal axis) and cost (vertical axis). When point A is in quadrant II, where the

intervention (A) is more effective and less costly than O, it will be the *dominant* alternative and is clearly preferred. In quadrant IV, where the intervention is less effective and more costly, alternative O is preferred. In quadrants II and III the choice will depend on the maximum cost-effectiveness ratio one is willing to accept, often referred as the cost-effectiveness threshold or the willingness to pay (WTP) (Drummond et al, 2005).

Figure 11: The cost-effectiveness plane



When the outcomes of alternative health care interventions or treatments are identical, a CEA is equivalent to a Cost-Minimization Analysis (CMA). However, because of a usual uncertainty around the measure of outcome, a full probabilistic CEA is often more preferred (Brazier et al, 2007).

4.2 Cost-Utility Analysis

In CUA, the incremental cost of a programme from a particular viewpoint is compared to the incremental health improvement attributable to the programme, where the health improvement is measured in quality-adjusted life-years (QALYs) gained, or possibly some variant, like disability-adjusted life-years (DALYs) gained. The results are expressed as a cost per QALY gained (Drummond et al, 2005).

CUA can be seen as a form of CEA in terms of comparing interventions as their cost per units of effect (Drummond et al, 2005). The unit of effect, a year in full health (QALY), is measured on an interval scale which combines length of life with health-related quality of life (HRQoL) (Brazier et al, 2007). This means that the QALY capture both morbidity and mortality, thus is a generic measure that is able to compare across studies. The following equation, where H = HRQoL and T = expected lifetime, shows how to calculate QALY.

Equation 2:

$$QALY = H * T$$

The number of QALY is calculated by multiplying a person's life expectancy by the value of the health-related quality of life measured on a scale between zero and one, where zero is dead and one is full health (Brazier et al, 2007). Some health states may be considered worse than death and will then have negative scores. Since the outcomes of any given intervention are uncertain, the probability must be taken into account to calculate the expected value of each possible outcome. Any QALY benefit has the same effect on preferences. This means that an increase of health from 0.1 to 0.3 is the same as an increase of health from 0.7 to 0.9, ten years of health at 0.5 is the same as five years of full health (which is one) and two people benefiting by five QALY each is the same as one person benefiting by ten QALY. There are various methods for measuring individual preferences, including visual analogue scale (VAS), standard gamble (SG) and time trade-off (Drummond et al, 2005).

Similar to CEA, the CUA approach is useful under budget constraints or thresholds, when decisions between interventions must be made. But importantly, when using the CUA approach, comparisons can be made between interventions with more than one kind of health outcome, including side effects, so it is a useful tool for decision-makers when and how to prioritize resources. It also have the advantages that interventions of the same

condition with different health outcomes can be compared against each other and interventions for different kinds of health problems with different health outcomes can also be compared.

4.3 Cost-Benefit Analysis

When using the CBA approach, both the cost and the benefits are measured in monetary units. This gives CBA the advantage, in contrast to CUA and CEA, of being a useful tool in, and across, all sectors of the economy. In short, an intervention is worthwhile if the benefits exceed the costs, meaning that the Net Social Benefit (NSB)>0 (Drummond et al, 2005). When policy makers are limited by a fixed budget, it is useful for them to know the NSB of a project to be able to rank the options and choose the "right" one.

One challenge is how to value, or translate, health benefits into monetary terms. There are three general, but different, approaches when valuing health outcomes (Drummond et al, 2005):

- The human capital approach (present value of future earnings)
- The revealed preferences approach (individual preferences regarding the value of increased health risk, also called wage-risk approach)
- The contingent valuation approach (stated preferences of WTP)

4.4 Cost-Consequence Analysis

There are arguments of whether CBA, CEA, and CUA are able to capture all relevant and legitimate concerns or not, for example some concerns that are related to equity and efficiency (Drummond et al, 2005). In a CCA, all the relevant concerns and factors are presented in the form of a table, and do not have a single number to enable a unique and complete ranking of different treatment options. It is then left to the decision maker to decide which treatment that is preferred. The problems of CCA is that it will not be clear how decisions actual would or should be made, since they will not be based on explicit values.

5. Epidemiological concepts and study design

Epidemiology is, in short, a science that primarily studies the patterns of disease in a population, and that seek to understand the causes, effects and burdens of disease (Bhopal, 2002). This knowledge is essential in healthcare policy, when planning to prevent and control disease, and to improve health. Epidemiology focuses foremost on the patterns of a population rather than on the single individual, since disease is influenced by the interaction and composition of individuals, and because epidemiology is highly dependable on demographic population data.

Measurement is a central feature of epidemiology (Rothman, 2002). There are several methods and measurements to apply when measuring the occurrence of disease and when studying the causes of disease. *Risk* or *incidence proportion* could be defined as the probability of an individual to develop a disease in a defined population and during a defined time period. If *A* represents the number of people developing disease during a time period, and *N* represents the total number of people during the same time period, the proportion *A / N* represents the average risk of disease in the population during that time period.

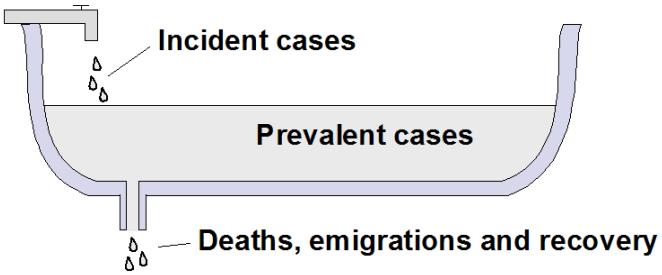
Risk (incidence proportion) = A / N

When measuring disease frequency in epidemiology, the *incidence rate* and the *prevalence rate* are the two principal measures. The incidence rate could be defined as the frequency of new occurrences of a disease in a population at risk of the disease during a period of time. The difference between incidence proportion and incidence rate is that the incidence rate is expressed as the number of new cases per unit of person-time at risk, for example per year, while incidence proportion only use time. Using the incidence rate handles situations where the amount of observation time differs between people, or when the population at risk varies with time.

Incidence rate = A / Sum of time periods

The prevalence rate could be defined as the number of occurrences of a disease in a population at risk of the disease either at a given point in time (point prevalence) or over a time period (period prevalence, lifetime prevalence). In short, the incidence rate focuses on the number of new occurrences while the prevalence rate focuses on all occurrences.

Figure 12: Incidence versus prevalence



Epidemiological studies often seek to make comparisons between populations groups, different places and over time (Bhopal, 2002). To see how the risk of a disease varies between populations, the *relative risk* (RR), which is the ratio of two incidence rates, can be calculated. More importantly, the RR is a useful tool when calculating the size of an effect of a risk factor on a disease. This is done by comparing the incidence rates between two population groups, one exposed to a specific risk factor, the other not. Although the formula for RR is simple, the interpretation is not. The two population groups could differ in many ways, not just by being exposed to a specific risk factor, which could affect the incidence rates for the disease. RR can never be calculated from a case-control study which do not provide data on incidence, but the *odds ratio* (OR) can be calculated and give a measure of the relative odds for being exposed to a causal factor in diseased and non-diseased individuals. The odds are the chances in favour of one event in relation to another event. In epidemiology, the odds are the chances of being exposed to a risk factor (or being sick) as opposed to not being exposed to a risk factor (or being sick). The OR is one set of odds divided by another. If there is no association the OR will be one. Table 3 shows how to understand and calculate RR and OR.

Risk factor	Diseased	Not diseased	Total
Present	A	B	A + B
Not present	C	D	C + D
Total	A + C	B + D	A + B + C + D

The incidence in the group with the risk factor = A / A + B
The incidence in the group without the risk factor = C / C + D
RR = (A / A + B) / (C / C + D)
OR = (A x D) / (C x B)

Table 3: Incidence rate, relative risk and odds ratio (Bhopal, 2002)

5.1 Biases and confounding

In epidemiology, a bias arises when errors affect comparison groups unequally, leading to false understanding about the patterns of disease (Bhopal, 2002). Biases are often categorized into three groups; *selection bias, information bias and confounding*. Bhopal agues that this list is incomplete, and that *hypothesis bias, intervention bias, interpretation bias,* and *publication bias* also should be included.

A biased hypothesis implies that a research question could affect one group more than the other, by not being neutrally stated. To pose the research question "Are men healthier than women?" is to be considered as a biased question. The way the question is stated reveals a presumption that this is the case, and could affect the study at a later state. The values and beliefs of the researcher should be revealed as rarely as possible, also for ethical reasons.

A selection bias is due to the method of collecting data, often the collection of samples. For convenience reasons, some population groups, for example volunteers, tend to be more used in studies than others. The problem is that volunteers may be different in their behaviour, attitudes, status, and more compared with those who do not volunteer, so only including volunteers in a study will not give a true picture. Some population groups are excluded from major studies for not speaking the language, being less accessible, or for belonging to a minority group. Also, some population groups tend to be excluded as a result from the

chosen source of a study population, for example the usage of the register of licensed drivers. A non-response bias is a form of selection bias where the subject chosen for a study do not participate. Since it is likely that these non-responders differ in characteristics from those that do respond, ignoring that could lead to selection biases, especially if the number of non-responders differs greatly in two groups being compared.

Confounding means that there is an error in the assessment of the association between a disease and a potential causal factor, meaning that there could be other variables (that is not considered in the study) causing the effect, rather than the postulated causal factor. Confounding often appears when comparing population groups that differ in characteristics. Randomization is one way to address the problem of confounding but it is no guarantee for avoiding it completely, especially in small and subgroup studies.

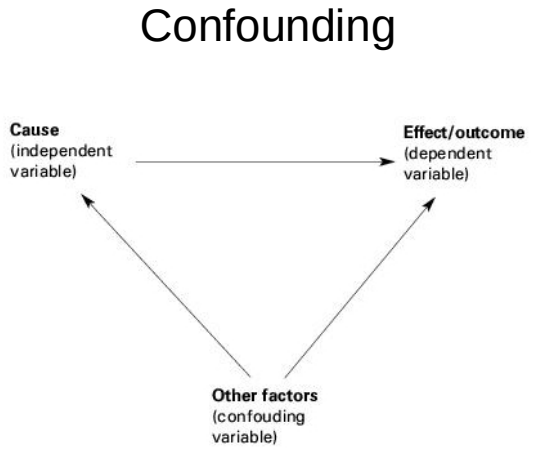


Figure 13: The relationship between the disease (dependent variable), the associated apparent risk (independent variable), and the confounding factor

The figure shows that the confounding factor, which is the true causal factor, is associated both with the apparent risk factor and the disease. One example could be a study that shows that alcohol (independent variable) is associated with lung cancer (dependent variable). By now we know that smoking is the main cause for lung cancer, but also that it is related to alcohol (people that drink alcohol tend to smoke more than people who don't drink alcohol). Smoking will then be the confounding factor, which is the true cause for lung cancer.

An information bias is a bias in measurement of exposure or outcome, and is a common problem. It can be caused by biological variations, inaccurate observations and tests, machine imprecision, variation in data collection, and more. Measurement errors could lead

to misclassification bias where a person is put in the wrong group. This is common in screening tests, where measurement errors are measured by the concepts of sensitivity and specificity.

The biases in interpretation- and publication of data are mostly related to the behaviour, interests and expertise of the researcher.

5.2 Study design

Epidemiological studies vary in its designs but share the same key purposes, which are to understand disease causation and burden of disease (Bhopal, 2002). Five classifications distinguish between descriptive and analytic studies, retrospective and prospective studies, observational and experimental studies, presence and absence of disease in the beginning of the study, and studies with a control group or not. There is great variation in how the different epidemiological study designs fit these classifications.

A *cross-sectional study* is an observational study that provides a "snapshot" of the patterns of diseases and risk factors in a representative part of the population at a point in time. The main research purposes are to measure prevalence of diseases, though also to seek associations between diseases and risk factors and to test or generate hypotheses. A cross-sectional study can be used to measure change in disease patterns and to evaluate interventions, by performing repeated studies in different time periods (repeated cross-sectional or panel design). Data about the past medical history of a general (well) population can be collected and show a wide spectre of diseases, but will then only give an indirect insight of the natural history. People that are institutionalized from severe diseases may be missed because they might not be on the sample list.

A *case-control study* is an observational study where one group of people with a disease are compared to another group of people without that disease (control group). The control group yields information about the expected risk factor profile in the population from which the case group is drawn. To be as representative as possible, the set of cases would ideally be incident cases, usually obtained from population registers and new cases identified in cohort studies. The control group should not have the same pattern of exposure to the cause, but they should be alike in the matter of other characteristics. The controls may be chosen to

match each case, for example in age and sex, to reduce the risk of confounding. Since some diseases develop over years, it is necessary to collect information on causal exposure from the past. The associations between a disease and a causal risk factor are measured by the difference in odds of being exposed to the potential causal factor in the case and the control group. The main research purpose is then to test whether the odd ratio is different from one.

A *cohort study* is a longitudinal study in which data are collected at two or more points in time from the same individuals, who has something in common, for example, smoking habits. The purpose is to investigate whether one or more exposures are related to later disease. A cohort study is then a prospective study that seeks to measure the incidence rate of a disease. An example; Two groups are identified in the base population, those who smoke and those who don't. These groups are tracked over time to identify the number of new cases of lung cancer in both groups, and to compare its incidence rates and find the relative risk. The result will provide us information about the impact smoking has on lung cancer, although the quality of the result will highly depend on the size and composition of the group, as well as the timeframe and quality of data. A cohort study can also be retrospective, where the exposure status is assembled from the past and the outcomes are explored in the present.

A *randomized clinical trial* is an experimental study where individuals are exposed or not exposed to an intervention based on a random process such that other causal factors are equally distributed among the two groups. The design is similar to that in a cohort study, with one significant difference, that the exposure status of the individuals has been deliberately chosen by the investigator. The purpose of the clinical trial is to see how the intervention or change in other exposure will influence the incidence of disease or other features of the natural history of disease. First a suitable population is defined, and then divided into one intervention group and one control group. To avoid confounding, the individuals should be randomly chosen for one group or the other. There are different variants of randomized clinical trails (RCT) including blinding and use of placebos. A placebo treatment for the control group has no effect on the disease itself, only a possible psychologically impact. To avoid bias, the information about who is in the intervention group or the placebo group is kept a secret from the participants, so called blinding. If the health carers also do no know, it is called double blinding, and triple blinding when the field investigator is added.

6. Research question and hypotheses

On the basis of the reviews of pituitary tumours, treatment, complications and different sealing techniques, I conclude that although pituitary tumours are rare and TSS is a reasonable safe procedure, one can not disregard that serious complications do occur and that the choice of sealing technique may affect the incidence of these complications as well as the outcome of those. The primary objective of this master thesis was to investigate the effectiveness of Tachosil® when used in TSS on pituitary tumours, by using Neuro-Patch® as a comparator. Earlier studies suggest Tachosil® (and TachoComb®) to be an effective sealing agent for this type of surgery (Czepko & Kwinta, 2006; Tamašauskas et al, 2008), and based on those study results I state the following hypotheses:

1) CSF-leaks

H_0: Tachosil® and Neuro-Patch® are equally effective in preventing CSF-leaks followed from TSS when removing pituitary tumours.

H_A: Tachosil® is more effective than Neuro-Patch® in preventing CSF-leaks followed from TSS when removing pituitary tumours.

2) Meningitis

H_0: Tachosil® and Neuro-Patch® are equally effective in preventing meningitis followed from TSS when removing pituitary tumours.

H_A: Tachosil® is more effective than Neuro-Patch® in preventing meningitis followed from TSS when removing pituitary tumours.

3) Diabetes insipidus

H_0: Tachosil® and Neuro-Patch® are equally effective in preventing diabetes insipidus followed from TSS when removing pituitary tumours.

H_A: Tachosil® is more effective than Neuro-Patch® in preventing diabetes insipidus followed from TSS when removing pituitary tumours.

4) Bleeding

H_0: Tachosil® and Neuro-Patch® are equally effective in preventing bleeding followed from TSS when removing pituitary tumours.

H_A: Tachosil® is more effective than Neuro-Patch® in preventing bleeding followed from TSS when removing pituitary tumours.

5) Fatality rate

H_0: Tachosil® and Neuro-Patch® are equally effective in preventing fatalities followed from TSS when removing pituitary tumours.

H_A: Tachosil® is more effective than Neuro-Patch® in preventing fatalities followed from TSS when removing pituitary tumours.

6) Resource use: Length of stay at the intensity care unit

H_0: The Tachosil® group and the Neuro-Patch® group have equal length of stay at the intensity care unit.

H_A: The Tachosil® group have shorter length of stay at the intensity care unit than the Neuro-Patch® group.

7) Resource use: Length of standard ward care

H_0: The Tachosil® group and the Neuro-Patch® group have equal length of stay at the standard ward care unit.

H_A: The Tachosil® group have shorter length of stay at the standard ward care unit than the Neuro-Patch® group.

7. Methods

7.1 Literature search

To get an insight into the relevant literature needed when conducting this study, I performed a literature search, focusing on articles published in the PubMed database. I used a combination of the three following keywords: *Pituitary tumour; Transsphenoidal surgery; Cerebrospinal fluid rhinorrhea.* These keywords were combined with additional terms such as: *Endoscopic surgery; Sella turcica repair; Tachosil®; Prevalence; Incidence; etc*. Also, relevant references mentioned in the identified articles were used.

Additionally, Nycomed provided me with articles and studies of Tachosil® used in several areas and purposes, and I have included these in my study. B. Braun Melsungen AG provided me with information on Neuro-Patch®.

7.2 Data collection from Ullevål University Hospital

Data for 82 patients who had undergone TSS for removing pituitary tumours at Ullevål University Hospital in the years of 2006-2008 were collected by an assistant resident during the second week of February in 2009 (Appendix 1). All neurosurgical operations at Ullevål are registered manually in operation protocols, and these protocols were searched through twice to identify the operations with operation code for TSS on pituitary tumours. When those patients were identified, their medical records were found in the Pasdoc-system, which is the EPJ used at Ullevål.

The size in millimetre of the tumour was measured on the MR-images taken prior to surgery. When a tumour was smaller than 10 mm it was classified as a microadenoma and otherwise a macroadenoma. When patients experienced vision affection, an examination was usually done by an ophthalmologist prior to surgery. In case of an acute surgery, the neurosurgeon performed the vision test. When there was suspicion of meningitis (fever, neck stiffness, sensitivity to bright light etc), a sample of the CSF was tested for glucose. If the concentration of glucose was lower than half of the concentration in the blood, it was taken

as a sign of meningitis. It may take some time before the test is analysed, so if there was strong suspicion of meningitis, antibiotic therapy was immediately given to the patient. The expert judgement of the physician was the basis for deciding when CSF-leaks and bleeding was present. All operations between 2006 and 2008 were performed by the same surgeon. The follow-up time of the number of deaths was within one month after the patient was discharged from the hospital.

7.3 Costs

All costs were measured in 2009 Norwegian Kroner (NOK), and VAT was excluded (Table 4). The costs that were identified measured and valued was the product costs of Tachosil® and Neuro-Patch®, and costs of stay at the Intensity Care Unit (ICU) and Standard Ward Care (SWC). Three different sizes of Tachosil® were used; 3 cm x 2.5 cm (NOK 514), 4.8 cm x 4.8 cm (NOK 1,440) and 9.5 cm x 4.8 cm (NOK 2,620). Two different sizes of Neuro-Patch® were used; 1.5 cm x 3 cm (NOK 369) and 4 cm x 5 cm (NOK 742). The mean sealing product cost used during an operation in the Neuro-Patch® group and in the Tachosil® group was calculated.

The cost of one day at the ICU in the Neurosurgical department at Ullevål University Hospital was NOK 27,000 and the cost of one day of SWC was NOK 4,800. The mean cost of a patient from the Neuro-Patch® group staying at the ICU (1.93*27,000) and the mean cost of SWC (7.93*4,800) were calculated, and the same calculations were made for the Tachosil® group (1.42*27,000 and 5.92*4,800).

The costs in the combination group and in the Duragen® group were not calculated. Due to limitation of available data, the part of the analysis which included costs was inadequate.

Table 4: Unit costs of cost items included in the study

Cost variable	Description	Cost (NOK)	Source
Tachosil®1	3 cm x 2.5 cm	514	Manufacturer (Nycomed)
Tachosil®2	4.8 cm x 4.8 cm	1,440	Manufacturer (Nycomed)
Tachosil®3	9.5 cm x 4.8 cm	2,620	Manufacturer (Nycomed)
Neuro-Patch®1	1.5 cm x 3 cm	369	Manufacturer (B. Braun)
Neuro-Patch®2	4 cm x 5 cm	742	Manufacturer (B. Braun)
ICU stay	One day stay at the Intensity Care Unit	27,000	The administration of the Neurosurgical department at Ullevål
SWC stay	One day of Standard Ward Care	4,800	The administration of the Neurosurgical department at Ullevål

7.4 Statistical tests

The patients were divided into four groups according to which sealing technique that were used during the operation. Differences between the groups in terms of patient characteristics, complications and number of reoperations were tested by a Chi-Square test, and were considered statistically significant when the *p*-value were <0.05. The differences in resource use were tested by a *t*-test, and were considered statistically significant when the *p*-value were <0.05.

Logistic regression analyses were performed to test the relationship between each complication (CSF-leak, meningitis, diabetes insipidus, bleeding and death) and various independent variables (age, sex, elective surgery, endoscope, size, vision affection, hormonal activity and Tachosil). The variables were coded as described in Appendix 1.

In binary logistic regression, we assume that the probability of the outcome (p) has the following functional form:

$$\text{Log } (p/1\text{-}p) = \beta_0 + \beta_1 X_1$$

Where β_0 denotes the constant of the regression equation while β_1 is a vector of regression coefficients and X_1 is a vector of covariates. The natural logarithm is:

$$e = 2.71828$$

All statistical tests were performed in the software program SPSS.

8. Results

8.1 Patient characteristics

The age of the 81 patients varied from 16 to 83 with a mean of 58 and a median of 63 (Table 5). There was a reasonably equal distribution of males and females in the patient group, 46% *versus* 54%. A macroadenoma was diagnosed in 86% of the cases, a hormonal active adenoma in 44% of the cases, and vision affection was detected in 57% of the patients. Endoscopic technique was used in 58% of the operations and 93% of the operations were elective. Many of the patients had various secondary diagnoses (Appendix 2), frequently more than one; 26% of the patients had no secondary diagnoses, 26% had one, 27% had two, 11% had three, and 9.9% of the patients had four or more secondary diagnoses.

Four different sealing techniques were used at Ullevål University Hospital during the years of 2006-2008. Neuro-Patch® was used on all patients in 2006 and on most of the patients in 2007. In total, 60 patients received treatment with Neuro-Patch®, 13 patients received Tachosil®, 8 patients received a combination of Neuro-Patch® and Tachosil®, and one patient received treatment with a third sealing product called Duragen®. The mean age was 49 in the Tachosil® group, 59 in the Neuro-Patch® group and 59 in the combination group. The proportion female was 31% in the Tachosil® group, 57% in the Neuro-Patch® group and 75% in the combination group. Patients with macroadenoma were reasonably equally distributed between the groups, as well as the number of patients undergone elective surgery. There were fewer patients experiencing vision affection (39% *versus* 62% and 50%*)* and fewer patients (31% *versus* 47% and 50%) who had a hormonal active tumour in the Tachosil® group than in the other two groups. Endoscopic technique was implemented at Ullevål first in the late part of 2006, and therefore only 43% of the operations in the Neuro-Patch® group were performed with that technique, whilst all patients in the other groups were operated with endoscopic technique. Overall, there were fewer patients with secondary diagnoses in the Tachosil® group. None of the differences in patient characteristics between the groups were statistically significant.

Table 5: Characteristics of the 81 patients according to sealing technique

	Neuro-Patch® (N = 60)	**Tachosil® (N = 13)**	**Neuro-Patch®/Tachosil® (N = 8)**	***P*-value**	**All (N = 81)**
Mean Age **Median Age** **Age range**	59.4 60.0 58 (25 - 83)	48.7 48.0 63 (16 - 79)	59.3 62.5 34 (45 - 79)		57.7 62.5 67 (16 - 83)
Female	56.7 %	30.8 %	75.0 %	0.110	54.3 %
Size of tumor > 10 mm	85.0 %	92.3 %	87.5 %	0.781	86.4 %
Vision –affection	61.7 %	38.5 %	50.0 %	0.285	56.8 %
Hormonal active	46.7 %	30.8 %	50.0 %	0.548	44.4 %
Elective surgery	91.7 %	100.0 %	87.5 %	0.492	92.6 %
Endoscope	43.3 %	100.0 %	100.0 %	0.000	58.0 %
No secondary diagnoses	23.3 %	38.5 %	25.0 %	0.376	25.9 %
One secondary diagnosis	23.3 %	38.5 %	25.0 %		25.9 %
Two secondary diagnoses	33.3 %	7.7 %	12.5 %		27.2 %
Three secondary diagnoses	10.0 %	15.4 %	12.5 %		11.1 %
Four or more secondary diagnoses	10.0 %	0.0 %	25.0 %		9.9 %

* When performing the Chi-Square test, the Duragen® group was excluded.

8.2 Health outcomes

The overall complication rate was 26%, with variations between the different types (Table 6). CSF-leak was present in 8.6% of the cases, meningitis in 6.2%, diabetes insipidus in 15%, bleeding in 8.6 %, other complications in 4.9%, and death within one month in 2.5% of the cases. Reoperations were performed when total tumour removal was not achieved or for other reasons. A patient was reoperated once in 11% of the cases, twice in 6.2%, and a third time in 1.2% of the cases.

The patients in the Neuro-Patch® group experienced a complication rate of 25%, which is similar to the patients in the Tachosil® group who had a complication rate of 23%. The patients receiving a combination of Neuro-Patch® and Tachosil® had a higher complication rate (38%). A CSF-leakage was detected in 8.3% of the cases in the Neuro-Patch® group, 7.7% in the Tachosil® group, and in 13% in the combination group. Meningitis was the complication with the lowest incidence rate in both the Neuro-Patch® group (5%) and the Tachosil® group (0%), but had fairly high incidence rate in the combination group (25%).

Diabetes insipidus had the highest incidence rate in all three groups; 10% in the Neuro-Patch® group, 23% in the Tachosil® group, and 38% in the combination group. Bleeding was considered as a complication in 8.3% of the patients in the Neuro-Patch® group, 7.7% in the Tachosil® group, and in 13% of the patients in the combination group. Other complications such as pneumonia was detected in 5% of the cases in the Neuro-Patch® group, 0% in the Tachosil® group, and in 13% of the cases in the combination group. In some cases, more than one complication was observed. Two patients died within one month after the patients was discharged from the hospital; one in the Neuro-Patch® group and one in the Tachosil® group. The differences between the groups in terms of complication rates were not statistically significant.

In the Tachosil® group, 7.7% of the patients were reoperated once, whilst no patients were operated a second or third time. 12% of the patients in the Neuro-Patch® group had one reoperation, 6.7% had a second reoperation, and no patients had a third operation. All the patients in the combination group that went through a first reoperation (13%) also went through a second and a third, hence only patients from the combination group were reoperated a third time. The differences between the groups in terms of a third reoperation was statistically significant ($p = 0.010$)

Table 6: Complications and reoperations according to type of sealing technique

	Neuro-Patch® (N = 60)	**Tachosil® (N = 13)**	**Neuro-Patch®/Tachosil® (N = 8)**	***P*-value**	**All (N = 81)**
Any Complication	25.0 %	23.1 %	37.5 %	0.726	25.9 %
CSF leak	8.3 %	7.7 %	12.5 %	0.917	8.6 %
Meningitis	5.0 %	0.0 %	25.0 %	0.053	6.2 %
Diabetes insipidus	10.0 %	23.1 %	37.5 %	0.079	14.8 %
Bleeding	8.3 %	7.7 %	12.5 %	0.917	8.6 %
Other complications	5.0 %	0.0 %	12.5 %	0.438	4.9 %
Death	1.7 %	7.7 %	0.0 %	0.399	2.5 %
One reoperation	11.7 %	7.7 %	12.5 %	0.910	11.1 %
Two reoperations	6.7 %	0.0 %	12.5 %	0.488	6.2 %
Three reoperations	0.0 %	0.0 %	12.5 %	0.010	1.2 %

8.3 Lengths of stay and costs

The mean ICU LOS in the Tachosil® group was 1.42 days and SWC LOS was 5.92 days, while the numbers were 1.93 and 7.93 in the Neuro-Patch® group (Table 7). There was no statistically significant difference between the sealing groups in terms of ICU LOS or SWC LOS. The mean cost of the sealing product was NOK 394 in the Neuro-Patch® group and NOK 1,261 in the Tachosil® group. The difference between the sealing groups according to mean costs of the sealing products used was statistically significant ($p<0.001$).The mean ICU cost of a patient in the Neuro-Patch® group was NOK 52,200 and NOK 38,250 in the Tachosil® group ($p=0.265$). The mean SWC cost in the Neuro-Patch® group was NOK 38,080 and NOK 28,400 in the Tachosil® group ($p=0.856$).

Table 7: Mean resource use according to type of sealing technique*

	Neuro-Patch®	**Tachosil®**	***P*-value**
ICU LOS **	1.93 days	1.42 days***	0.265
SWC LOS**	7.93 days	5.92 days***	0.856
Cost Sealing product	394	1,261	0.000
Cost ICU	52,200	38,250***	0.265
Cost Standard Ward Care	38,080	28,400***	0.856

* The resource use comparisons were only performed for the Neuro-Patch®- and Tachosil® groups because of few patients in the remaining two groups.

** ICU LOS and SWC LOS represent data (the mean) from the first surgeries and in some cases also second and third surgeries.

*** One patient in the Tachosil® group died during surgery; hence there is no data on ICU LOS or SWC LOS for that patient.

8.4 Logistic regression

The logistic regression equation for the occurrence of complications was expressed as:

$$\text{logit}(p) = \beta_0 + \beta_1 * \text{Age} + \beta_2 * \text{Sex} + \beta_3 * \text{ElSurg} + \beta_4 * \text{Endoscope} + \beta_5 * \text{Size} + \beta_6 * \text{VisAff} + \beta_7 * \text{HormAct} + \beta_8 * \text{Tachosil®}$$

Where p is the probability of a complication.

In the logistic regression analysis of the odds for diabetes insipidus (Table 8), the odds ratio was 0.936 for age (95% CI 0.889-0.985, *p*=0.012) while the other covariates were not significant. In none of the other regression analyses of the other complications, there were any significant covariates (see Appendix 3).

Table 8: Logistic regression on diabetes insipidus and explanatory variables

Variable	***P*-value**	**Odds ratio**	**95.0 % C.I**	
			Lower	**Upper**
Age (years)	0.012	0.936	0.889	0.985
Sex (0 = male 1 = female)	0.784	1.231	0.278	5.462
Elective surgery (0 = no 1 = yes)	0.576	2.034	0.169	24.489
Endoscope (0 = no 1 = yes)	0.187	2.989	0.587	15.217
Size (0 = micro 1 = macro)	0.384	3.437	0.213	55.399
Vision affection (0 = no 1 = yes)	0.330	2.306	0.429	12.382
Hormonal active (0 = no 1 = yes)	0.654	1.418	0.308	6.538
Tachosil® (0 = no 1 = yes)	0.738	0.705	0.091	5.464
Constant	0.578	0.260		

9. Discussion

The results of the study indicate that there is no difference in the risk of complications between the Neuro-Patch® group and the Tachosil® group, nor is there any cost difference except for the sealing products itself. However, there are several weaknesses of the study that need to be considered.

9.1 Weaknesses

9.1.1 Sample size and distribution

The sample was limited in the number and unbalanced in that the number of Neuro-Patch® patients was much greater than the number of Tachosil® patients, and also there was a group of patients receiving a combination of Tachosil® and Neuro-Patch® in addition to a fourth group where one patient received Duragen®. Hence, the patients were not equally distributed between the groups.

Another limitation of the study is that the Neurosurgical department during the study period changed sealing techniques as well as operation technique, and it is difficult to disentangle the consequences of the two changes.

9.1.2 Fatality rate

The follow-up time of counting the number of deaths was one month after the patient was discharged from the hospital in order to have the same follow up period for all patients. Consequently, several deaths that occurred later are not included in the study. Ideally, a Cox regression analysis could have solved the problem.

Also, there was no information in the data set on the causes of death. Hence, there is a possibility that causes of deaths had nothing to do with complications followed from the operations.

9.1.3 Omitted variables

To evaluate the effectiveness of Tachosil®, information on the length of the operations would have been preferred. Unfortunately, this information was available in less than 60% of the Neuro-Patch® patients and less than 85% of the Tachosil® patients.

In terms of reoperations, the registration on ICU LOS and SWC LOS was not consistent. If a patient was discharged from the hospital, and then hospitalized again for a reoperation, no information on the length of stay was registered. However, if the patient was reoperated before being discharged, the total length of stay was captured. Therefore, the calculated mean of ICU LOS and SWC LOS was not accurate.

9.1.4 Costs

Due to the inaccurate data on ICU LOS and SWC LOS, the cost of hospitalization would also be inaccurate. More importantly, many cost items that should have been included in the study (to provide a true picture of the costs involved) were not identified (costs of GP visits, surgery, other treatment costs, personal costs, and more). The study results should therefore not be used to make inferences about differences in total costs across the sealing techniques.

9.2 Strengths

Since the sample used for this study were identified in operation protocols, there is reason to believe that all patients that underwent TSS for removing pituitary tumours at Ullevål University Hospital in the years 2006-2008 were identified.

Several characteristics of the patients (age, sex, size of tumour and more) were captured, as well as the complication rates and sealing technique that was used during the operations.

9.3 Interpretation of the results

The stated hypotheses have been tested by statistical tests such as logistic regressions, Chi-Square tests and *t*-tests. None of the alternative hypotheses were confirmed and the null hypotheses can not be rejected. Although it would be tempting to discuss indications of possible differences in terms of complications and length of stay between the sealing groups, I will not do that.

9.4 Findings of other studies

The only comparable study, is the study by Tamašauskas et al. Tachosil® was used as a sealing agent (in combination with Surgicel®) after removing pituitary tumours with TSS, and when intraoperative CSF-leaks were present. The postoperative complication rate for the Tachosil® group was 14%, compared to a total complication rate of 23% in this study. The registration of complications was not identical, however. One problem when comparing the studies is that Tachosil® in the Tamašauskas study, only was used when intraoperative CSF-leaks were present, while in this study it was used even when the complication was not present. Also, CSF-leaks were not classified as intra- or postoperative in the data set used for this study, as in the Tamašauskas study. In fact, if including intraoperative CSF-leaks as a complication, the complication rate would have been much higher than 14%. Tamašauskas concluded that Tachosil® was the more effective sealing agent compare to the other method used. No such conclusions can be made from this study.

9.5 Implication and conclusion

The results of this study do not confirm any of the hypotheses, and do not provide any evidence that Tachosil® is superior in terms of complications or length of stay.

10. Appendix

Appendix 1: List of variables

Variables extracted from 82 patient records at Ullevål University Hospital

Variable name	Explanation	Type	Coding
RegNr	Registration number	Numerical	200xxx
Age	Age of the patient	Numerical	Years
Sex	Sex of the patient	Categorical	1 = Female 0 = Male
MainDiag	Main diagnose	Categorical	ICD-10 coding
SecondDiag	Secondary diagnoses	Categorical	ICD-10 coding
Size	Size of the tumour	Categorical	1 = Macro 0 = Micro
VisAff	Vision affection	Categorical	1 = Yes 0 = No
HormAct	Hormonal active tumour	Categorical	1 = Yes 0 = No
ElSurg	Elective surgery	Categorical	1 = Yes 0 = No
SurgCode	Surgery code	Categorical	Operation code
SurgTime	Length of surgery in minutes	Numerical	Minutes
ICULOS	Total length of stay at the intensity care	Numerical	Days
SWC LOS	Total length of stay at the standard ward care unit	Numerical	Days
TotalLOS	Total length of stay at the hospital	Numerical	Days
Endoscope	Use of endoscope	Categorical	1 = Yes 0 = No
SealingTech	Sealing technique	Categorical	1 = Tachosil® 0 = Neuro-Patch® 2 = Tach/Neuro 3 = Duragen®
DRG	DRG code	Categorical	DRG coding
ProdCm	Cm of the sealing product	Categorical	Tachosil®; 1 = 9.5cm x 4.8 cm 2 = 3.0cm x 2.5cm 3 = 4.8cm x 4.8cm Neuro-Patch®; 1 = 1.5cm x 3cm 2 = 4cm x 5cm
Complications	Complications	Categorical	1 = Yes 0 = No
CSFLeak	Cerebrospinal fluid leakage	Categorical	1 = Yes 0 = No
Bleeding	Bleeding	Categorical	1 = Yes 0 = No
Diabetes	Diabetes insipidus	Categorical	1 = Yes

			0 = No
Meningitis	Meningitis	Categorical	1 = Yes 0 = No
OtherCompl	Other complications	Categorical	1 = Yes 0 = No
Reoper	Reoperation	Categorical	1 = Yes 0 = No
Death	Death registered within a timeframe of one month	Categorical	1 = Yes 0 = No

Appendix 2: ICD-10 codes

The ICD-10 codes are classified into sub-categories[14]. The table shows the prevalence of the present sub-categories in the four sealing groups

	Neuro-Patch® (N = 60)	**Tachosil® (N = 13)**	**Neuro-Patch®/Tachosil® (N = 8)**	**Duragen® (N = 1)**
Neoplasm	100.0 %	100.0 %	100.0 %	100.0 %
Endocrine, nutritional and metabolic diseases	41.7 %	23.1 %	62.5 %	0.0 %
Diseases of the circulatory system	36.7 %	23.1 %	37.5 %	0.0 %
Injury, poisoning and certain other consequences of external causes	8.3 %	7.7 %	12.5 %	0.0 %
Diseases of the ear and mastoid process	1.7 %	0.0 %	0.0 %	0.0 %
Diseases of eye and adnexa	1.7 %	0.0 %	0.0 %	0.0 %
Diseases of the nervous system	10.0 %	15.4 %	25.0 %	100.0 %
Diseases of the respiratory system	11.7 %	0.0 %	0.0 %	0.0 %
Diseases of the musculoskeletal system and connective tissue	11.7 %	0.0 %	12.5 %	100.0 %
Diseases of the digestive system	3.3 %	0.0 %	12.5 %	0.0 %
Congenital malformations, deformations and chromosomal abnormalities	1.7 %	0.0 %	0.0 %	0.0 %
Certain infectious and parasitic diseases	1.7 %	0.0 %	0.0 %	0.0 %
Factors influencing health status and contact with health services	0.0 %	15.4 %	0.0 %	0.0 %
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	0.0 %	7.7 %	0.0 %	0.0 %
Diseases of the genitourinary system	1.7 %	0.0 %	0.0 %	100.0 %
Mental and behavioural disorders	1.7 %	0.0 %	12.5 %	0.0 %

[14] International Statistical Classification of Diseases and Related Health Problems. 10th Revision. Version for 2007. Extracted from WHO.

Appendix 3: Logistic regression

Logistic regression on CSF-leak and explanatory variables

Variable	P-value	Odds ratio	95.0 % C.I	
			Lower	Upper
Age	0.537	0.976	0.905	1.054
Sex	0.392	2.222	0.358	13.812
Elective surgery	0.999	2.892E8	0.000	
Endoscope	0.276	3.116	0.404	24.061
Size	1.000	3.948	0.000	
Vision affection	0.153	0.277	0.048	1.607
Hormonal active	0.998	0.000	0.000	
Tachosil	0.270	0.177	0.008	3.828
Constant	0.999	0.000		

Logistic regression on bleeding and explanatory variables

Variable	P-value	Odds ratio	95.0 % C.I	
			Lower	Upper
Age	0.167	0.956	0.896	1.019
Sex	0.054	0.082	0.006	1.049
Elective surgery	0.999	1.022E8	0.000	
Endoscope	0.182	0.231	0.027	1.988
Size	0.999	1.106E8	0.000	
Vision affection	0.556	0.520	0.059	4.581
Hormonal active	0.491	0.500	0.069	3.595
Tachosil	0.485	0.334	0.015	7.243
Constant	0.999	0.000		

Logistic regression on meningitis and explanatory variables

Variable	P-value	Odds ratio	95.0 % C.I	
			Lower	Upper
Age	0.050	0.905	0.818	1.000
Sex	0.269	0.208	0.013	3.358
Elective surgery	0.999	4.924E8	0.000	
Endoscope	0.997	4.076E8	0.000	
Size	0.576	0.281	0.003	24.073
Vision affection	0.811	0.747	0.068	8.157
Hormonal active	0.149	0.071	0.002	2.578
Tachosil	0.998	0.000	0.000	
Constant	0.998	0.000		

Logistic regression on death and explanatory variables

Variable	P-value	Odds ratio	95.0 % C.I	
			Lower	Upper
Age	0.959	1.003	0.880	1.144
Sex	0.996	0.000	0.000	
Elective surgery	0.999	0.000	0.000	
Endoscope	0.996	0.000	0.000	
Size	1.000	1.007	0.003	
Vision affection	0.997	0.000	0.000	
Hormonal active	0.998	0.000	0.002	
Tachosil	0.997	4.910E7	0.000	
Constant	0.999	4.094E13		

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